REMARKS

I. Introduction

The following remarks respond to the Office Action dated June 10, 2005. Claims 28-30, 48-50 and 54-57 are pending. Re-examination and re-consideration of the application is requested.

II. Objections and Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

On pages 2-7 of the Office Action, claims 28-30, 48-50 and 54-57 were rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

A. Claims Rejected Under 35 U.S.C. §101.

The pending claims are directed to isolated antibodies which bind to a PRO285 polypeptide, a member of the Toll protein family.

Applicants' disclosure teaches that comparative homology analyses and functional data from Toll family members indicate that PRO285 polypeptide signalling activates NF-κB, an event which leads to the expression of the inflammatory cytokines IL-1, IL-6 and IL-8. See, e.g. page 13, lines 13-25. Applicants' disclosure further teaches that antibodies to the PRO285 polypeptide can act as agonists or antagonists of NF-κB signalling and can therefore be used in methods designed to modulate the expression of genes controlled by NF-κB. See, e.g. page 13, lines 6-25.

As is known in the art, methods designed to modulate the expression of IL-1, IL-6 and IL-8 (e.g. via NF-κB activation) can be used in a variety of contexts. For example, reagents which induce the expression of IL-1, IL-6 and IL-8 are used in the topical treatment of warts (see, e.g. Beutner et al., Am. J. Med. 102 (5A) 28-37 (1997), a copy of which is provided as Attachment B). The specification further teaches that antagonistic anti-PRO285 antibodies may be used in pathologies characterized by an overexpression of IL-1, IL-6 and IL-8 (i.e. septic shock). See, e.g., page 37, lines 10-29. Consequently, one of skill in the art is familiar with circumstances where it is desirable to either stimulate or inhibit the activities mediated by PRO285.

In support of their asserted utility, Applicants provided a declaration under 37 CFR 1.1.32 by J. Fernando Bazan which states that one skilled in the art would reasonably understand that PRO285 can induce the expression of NF-κB-controlled genes and that antibodies to PRO285 can be made and used in accordance with routine techniques to modulate such activity. The utility of the claimed

subject matter is further validated by recent reports which confirm that molecules that bind to PRO285 can be used to modulate the expression of NF-κB-controlled genes. See e.g. Jurk et al., Nature Immunology 3(6), 499 (2002), a copy of which was provided with the response dated 12/9/2003.

In the outstanding Office Action, the Examiner rejects the pending claims, stating that the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

Applicants respectfully traverse this rejection because the utility asserted for the claimed subject matter would be considered specific, substantial and credible by the skilled artisan. For example, the use of agonistic and antagonistic antibodies as reagents to modulate the biological activities of a target receptor molecule is well known practice in the art. It is also known in the art that NF-κB controls the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a number of pathological syndromes including septic shock. While the association of PRO285 with NF-κB activation is based on a homology analysis, this technique is an art accepted method which is specifically designed to identify functional relationships based upon similarities in amino acid sequences. In support of the homology analysis and the asserted utility, Applicants provided an opinion of a qualified expert stating that one of skill in the art would find credible Applicants teaching that PRO285 can induce the expression of that IL-1, IL-6 and IL-8 (NF-κB-controlled genes) and that antibodies to PRO285 can be made and used in accordance with routine techniques to modulate the expression of these inflammatory cytokines. In addition, as noted above, the Jurk et al. reference teaches that PRO285 binding molecules do in fact modulate the expression of NF-κB-controlled genes.

Applicants respectfully disagree with the Examiner's assertions because artisans do in fact understand the usefulness of methods which modulate the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a number of pathological syndromes including septic shock (as described at page 6, lines 9-12). While the Examiner also asserts that the specification fails to teach how anti-receptor antibodies can modulate receptor activity (i.e. PRO285 activity), Applicants note that (as described at page 13, lines 6-25) the use of antibodies in such methods is well known in the art and would be considered credible by the skilled artisan. Moreover, while the Examiner disputes the expert's opinion, arguing for example that "of the six essential

residues for IL-R1 signaling domain, only two are conserved in PRO285", Applicant's once again point out that the expert's opinion on the significance of the homology is in fact correct as shown by the disclosure in Jurk et al. (which teaches that PRO285 binding molecules do in fact modulate the expression of NF-κB-controlled genes). While the issue is indisputable in view of the disclosure of Jurk et al., Applicants further note that the guidelines state that office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned (section 4 of the guidelines promulgated by the Patent Office).

As noted above, the utility asserted for the claimed subject matter: (1) is readily understood by a skilled artisan; (2) conforms to known principles in this art; and (3) is acknowledged in opinion from a qualified expert. Consequently, the asserted utility would be considered credible by a person of ordinary skill in the art. In the instant situation, the Patent Office does not meet the requisite burden of proving that one of ordinary skill in the art would doubt the asserted utility. In particular, the guidelines promulgated by the Patent Office for the examination of applications for compliance with the utility requirement of 35 USC 101 and 35 USC 112, first paragraph dictate that if the assertion would be considered credible by a person of ordinary skill in the art, the Patent Office must not impose a rejection based on lack of utility. Only after an examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicants (see, e.g. M.P.E.P. 2164.07). In the instant case, the PTO fails to meet this burden. For at least the reasons above, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §101.

B. Rejection under 35 U.S.C. §112, First Paragraph.

In rejecting the claims under 35 U.S.C. §112 at page 7 of the outstanding office action the Examiner further asserts that since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully traverse the rejection because those of skill in the art will understand from the instant application and the state of the art that Applicants' invention has a specific, substantial and credible asserted utility. Consequently, one skilled in the art clearly would in fact

know how to use the claimed invention without undue experimentation. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §112 first paragraph.

III. Rejection under 35 U.S.C. §102(b)

On pages 7-8 of the Office Action, claims 28 and 48 were rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri). The Patent Office states that Ruggeri et al. disclose a 19 residue platelet membrane glycoprotein Ib peptide that matches SEQ ID NO: 2 at positions 704-712 (9 amino acids) and that at page 19 and in claim 65, antibodies to such peptides are disclosed and claimed. In view of this disclosure in Ruggeri, the Patent Office asserts "one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285" (Office Action dated October 26, 2004). In making this rejection, the Patent Office explicitly notes that this is anticipation via inherency and that "[I]t is not necessary that Ruggeri have any knowledge of PRO285 for anticipation to be found" (Office Action dated June 9, 2003, paper #22).

In response to the outstanding rejection under 35 U.S.C. §102(b), Applicants first note that polypeptides such as the 1049 amino acid PRO 285 recited in claim 28 do not occur in nature in a 2-dimensional form where every single amino acid residue is exposed and able to interact with proteins such as antibodies. Instead, polypeptides are known to fold in three dimensions. As is known in the art, the three dimensional conformation of a polypeptide dictates which antigenic determinants are exposed at the exterior of the polypeptide and are therefore capable of being bound by antibodies. The three dimensional conformation of a polypeptide also dictates the precise structure of its antigenic determinants that are recognized with such exquisite precision by antibodies.

Applicants traverse the outstanding rejection because the Ruggeri reference fails to provide a disclosure which places one in possession of the invention on which a patent is sought. For example, the Ruggeri reference fails to provide a disclosure that allows one to discern whether antibodies raised against the platelet membrane glycoprotein Ib peptide will bind to a completely different protein, for example "a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO:2". Applicants further note that the Patent Office's position that antibodies raised against the platelet membrane glycoprotein Ib peptide will bind to the completely different protein recited in the claims is based upon conjecture and may not in fact be true. For example, the 9 amino acids in PRO 285 that have identity to the 9 residue segment in platelet membrane glycoprotein Ib

peptide disclosed in Ruggeri occur at positions 704-712, a region in PRO 285 that is flanked by hundreds of other amino acid residues recited in the claims. These hundreds of flanking PRO 285 amino acid residues may assume a three dimensional conformation that physically prevents antibodies raised against the platelet membrane glycoprotein Ib peptide from contacting this segment of 9 amino acids in PRO 285. The Ruggeri disclosure however fails to provide the information that allows an artisan to discern this does or does not occur.

The Ruggeri reference further fails to teach that three dimensional conformation of the antibody binding site(s) on the 19 residue platelet membrane glycoprotein Ib peptide is serendipitously reproduced on for example "a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO: 2". In this context, a side by side comparison of flanking residues (e.g. the 6 C-terminal residues that are covalently attached to the identical 9 amino acid segments in these two polypeptides) shows the presence of two charged amino acid residues in the PRO285 protein (i.e. glutamic acid and arginine at positions 716 and 717 respectively), residues that are absent in the platelet membrane glycoprotein Ib peptide sequence. These observed differences in the chemical properties of the side chains of the C-terminal amino acid residues that flank the 9 amino acid segments in these different proteins provides evidence that the conformations of the respective antigenic determinants in these molecules are likely to be dissimilar. This difference in the platelet membrane glycoprotein Ib peptide and PRO 285 flanking sequences therefore provides evidence that antibodies generated using the platelet membrane glycoprotein Ib peptide will not cross-react with the PRO285 polypeptides recited in the claims. Applicants' attorney acknowledges however that this is merely conjecture on his part and that the Ruggeri disclosure simply fails to provide the information that allows an artisan to actually discern whether this does or does not occur.

The unpredictable folding of the 19 residue platelet membrane glycoprotein Ib peptide and the PRO 285 polypeptides recited in the claims prevents the Ruggeri disclosure from satisfying the legal standard for a finding of anticipation because for example it is not possible to discern if antibodies raised against platelet membrane glycoprotein Ib peptides will cross-react with the PRO285 polypeptides recited in the claims. While the Patent Office asserts that the Ruggeri disclosure anticipates the claimed invention via inherency because "one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285" (Office Action dated October 26, 2004), Applicants respectfully note that the Patent Office's conjecture as to what an antibody raised

against Ruggeri's peptide will or will not bind is an improper basis for a finding of anticipation. In particular, courts find that "anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product". See, e.g. *Ex parte* Standish, 10 USPQ2d 1454, 1457 (Bd. Pat. App. & Int'f 1989). Instead, courts find that a claim is anticipated only if each and every element set forth in the claim is found in a prior art reference. See, e.g. *Verdegaal Bros. V. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The prohibition on using conjecture as a basis for a finding of anticipation is further articulated in the case law pertaining to anticipation via inherency. In particular, when articulating the legal requirements for a finding of anticipation via inherency, courts state that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See, e.g. M.P.E.P. 2112 and *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). Instead, to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 20 USPQ 2d 1749.

The outstanding rejection fails to meet the legal requirements for a finding of anticipation because it is explicitly predicated on a conjectured probability, i.e. that one would "reasonably expect" an antibody raised against a platelet membrane glycoprotein Ib peptide to crossreact with the PRO285 polypeptides recited in the claims. The outstanding rejection is not based on a showing that the claimed subject matter is in fact disclosed in the Ruggeri reference. Consequently this rejection is contrary to the legal requirements for a finding of anticipation (e.g. as articulated in *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d at 1749). For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §102(b).

IV. Rejection under 35 U.S.C. §103(a)

At page 8 of the Office Action, claims 29 and 49 were rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri in view of Coughlin, U.S. Patent No. 5,256,766 (Coughlin). In addition, claims 50 and 54 were rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri in view of Coughlin and further in view of Ladner et al., U.S. Patent No. 4,946,778 (Ladner).

As the Ruggeri disclosure fails to meet the legal requirements for anticipation via inherency, this reference cannot properly be combined with U.S. Patent No. 5,256,766 and/or U.S. Patent No. 4,946,778 in order to suggest the subject matter recited in claims 29, 49, 50 and 54. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. 103(a).

V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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